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|----------|--------------|
| MERTZ, P | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

08/927,939

Applicant(s)

Grainger et al

Examiner

Prema Menz-

Group Art Unit

1646

---The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address---

Period for Response

A SHORTENED STATUTORY PERIOD FOR RESPONSE IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a response be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for response is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to respond within the set or extended period for response will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

- ☒ Responsive to communication(s) filed on 2-16-99
- ☐ This action is FINAL.
- ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- ☒ Claim(s) 1 - 41 ☒ are pending in the application.
- Of the above claim(s) 2, 13 - 41 ☒ are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 1, 3 - 12 ☒ are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
 - ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been received.
 - ☐ received in Application No. (Series Code/Serial Number) _____.
 - ☐ received in this national stage application from the International Bureau (PCT Rule 1.7.2(a)).

*Certified copies not received: _____

Attachment(s)

- ☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4, 6
- ☒ Notice of References Cited, PTO-892
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Interview Summary, PTO-413
- ☐ Notice of Informal Patent Application, PTO-152
- ☐ Other _____

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DETAILED ACTION

1. The preliminary amendment (Paper No.8, 2/16/99) has been entered in part because entries at page 10, lines 11-13 of the specification were not on the designated lines.

Restriction/Election

2. Applicant's election with traverse of Group I (claims 1 and 3-12) and species peptide 3(3-12)[MCP-1] in Paper No.8 (2/16/99) is acknowledged. The traversal is on the ground(s) that the restriction is improper since the examiner has not shown that examination of chemokine peptide 3 protein of Group I with the method of using the protein of Group VII, and a nucleic acid molecule encoding chemokine peptide 3 of Group III, and a method of preventing or inhibiting an indication associated with a chemokine-induced activity comprising administering to a mammal a nucleic acid molecule encoding chemokine peptide 3 or the complement of a nucleic acid molecule encoding chemokine peptide 3 of Group XI and a method of preventing or inhibiting an indication associated with a chemokine-induced activity comprising administering to a mammal a nucleic acid molecule encoding chemokine peptide 2 or the complement of a nucleic acid molecule encoding chemokine peptide 2 of Group XII, are independent or distinct inventions or would entail a serious burden. This is not found persuasive because the searches for the 5 Groups would not overlap, the inventions being classified in different classes and subclasses. Applicants are directed to MPEP 808.02 which states that "Where the related inventions as claimed are shown to be distinct and under the criteria of MPEP 806.05 (c-I), the examiner in order to establish reasons for insisting upon restriction, must show by appropriate explanation one of the following: 1) Separate classification thereof." In the instant case,

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the different Groups are classified in different classes and subclasses. In the case of Groups XI and XII, the Groups are independent and distinct, each from the other, because the methods are practiced with materially different products which are structurally and chemically different, the novelty of the inventions lying in the products being administered and not the processes. The only feature in common in the instant inventions is "a method of preventing or inhibiting an indication associated with a chemokine-induced activity", which does not constitute the special technical feature lacking from the prior art because this method can be used with a composition other than the instant products such as an antibody to the specific chemokines. Distinctness is further shown because each of these products in each method can be made and used without any one or more of the other products. The products in the different Groups are physically, chemically and biologically distinct from each other, and if patentable would support separate patents. Furthermore, separate search terms would be required for searching the literature, eg. a search of the literature for an association of chemokine peptide 3 in the instant method would not necessarily reveal art for an association of chemokine peptide 2 in the instant method.

The test for propriety of restriction is not whether the inventions are related but rather whether they are distinct and whether it would impose a burden on the examiner to search and examine multiple inventions in a single invention. Since Group I and Group VII are related as product and method of use, the inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using

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that product (M.P.E.P. § 806.05(h)). In the instant case the polypeptide can be used in a materially different process, such as in the generation of antibodies.

Lastly the inventions are distinct because a search of the literature for chemokine peptide 3, would not be expected to reveal art for a method of treatment with the peptide, which searches are extensive requiring separate searches which would be unduly burdensome.

Having shown that these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and recognized divergent subject matter as defined by MPEP § 808.02, the Examiner has *prima facie* shown a serious burden of search (see MPEP § 803). Therefore, an initial requirement of restriction for examination purposes as indicated is proper.

The Groups as delineated in the restriction requirement (Paper No. 5, 9/11/98) are patentably distinct one from the other such that each invention could, by itself, in principle, support its own separate patent (as shown by the arguments put forth in the written restriction requirement).

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 2 and 13-41 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 8 (2/16/99).

Specification

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4. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim objections

5. Claims 3-12 are objected because of the following informalities:

Claims 3, 4, 5, 7, 9-12 are objected to because the full meaning of an acronym should be stated at its first use in any claim.

Claims 6 and 8 are objected to because they are dependent on non-elected claim 2.

6. Bracketing or underlining are commonly used to indicate amendments or changes in the claims as provided in 37 CFR 1.121(a)(2)(ii) and are normally not intended to be printed in the published patent. In instant claims 4-5 and 12, applicant has used brackets “[” and “]” in such a manner that it is unclear to the examiner whether the brackets are intended to appear in the patent. The use of these brackets is unclear because the brackets as used by Applicants are not intended to indicate amendments or changes in the claims as provided by 37 CFR 1.121(a)(2)(ii). If underlining and/or bracketing is intended to appear in the claims in the published patent, such intention must be clearly indicated in applicant's reply to this notice.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

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Claims 1, 3-10 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims embrace a chemokine as it occurs *in vivo*. In the absence of a specific definition of chemokine peptide 3 in the instant specification, the claims encompass an entire chemokine as it occurs in nature is claimed. However, since it would that applicants do not intend to claim a naturally occurring product, amending the claim to require the hand-of-man would obviate this rejection e.g. an isolated and purified chemokine...

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8a. Claims 1, 3-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the human chemokine peptides of amino acid sequences set forth in SEQ ID NO:1, 7-14, and CRD of the chemokine peptide set forth in SEQ ID NO:14, does not reasonably provide enablement for "all" chemokine peptide 3 and variants or derivatives thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

With respect to claim 1, as recited, what is claimed in the instant invention broadly encompasses "all" chemokine peptide 3. The specification is non-enabling for the unlimited number

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of compositions comprising such a chemokine, and which are encompassed by the scope of the claim. Since no material limitations for chemokine peptide 3, have been recited in the claim, the claim encompasses every conceivable structure (means) for achieving the stated property (result). Therefore, any and all chemokine peptides, are encompassed by the scope of the claim. The claimed invention encompasses compositions not envisioned or described in the specification, and neither does the specification disclose how these claimed compositions can be distinguished from each other. The specification only enables the peptides set forth in Table 6, page 106 of the specification, peptides having the amino acid sequences shown in SEQ ID NO:1, 7-14, the peptides having specific characteristics and properties. These properties may differ structurally, chemically and physically from other known peptides. By application of the factors set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), which include (1) quantity of experimentation, (2) guidance presented, (3) the predictability of the art, and (4) the breadth of the claims, in the instant application, the quantity of experimentation to determine which other peptides, are encompassed by the scope of the claims is practically infinite and the guidance provided in the specification very little, thereby rendering the results of the assays taught in the specification unpredictable (see pages 97-103, Example 1). Therefore, it would require undue experimentation to determine which peptides having the desirable biological activity of chemokine peptide 3, would be encompassed by the scope of the claims. The disclosure of the peptides in Table 6, page 106, is clearly insufficient support under the first paragraph of 35 U.S.C. § 112 for claims which encompass every and all polypeptides, including variants and

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derivatives thereof. In In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), the Courts have held that:

"Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since some improvements while unobvious from his teachings, are still within his contribution; since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that the scope of the claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."

Furthermore, the amount of embodiments corresponding to the desirable peptides, may be innumerable, and the enabled embodiments amount to only those set forth in Table 6, page 106. Therefore, there are substantial scientific reasons to doubt the scope of enablement, as set forth above. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe any other peptides other than those whose amino acid sequences are shown in SEQ ID NO:1, 7-14, and since it is deemed to constitute undue experimentation to determine all the others, the disclosure is not commensurate with the scope of the claims. Therefore, Applicants are not enabled for chemokine peptides having anything less than the amino acid sequences shown in SEQ ID NOS:1, 7-14.

Applicants have disclosed formula (I) (page 3, line 13) for a preferred embodiment of chemokine 3. However, based on formula (I) which is a consensus sequence, not every embodiment

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encompassed by the claims would be expected to function as desired, nor could one of skill in the art be able to predict which of the embodiments encompassed by the scope of the claims, would function as expected. Since a vast majority of the embodiments encompassed by the scope of the claims would be non-naturally occurring, and the working embodiments are those peptides whose amino acid sequences are shown in SEQ ID NO:1, 7-14, the instant specification is non-enabling for the breadth of the claims.

With respect to claims 1, 4, 11-12, which recite “variant” or “derivative”, these limitations are non-enabled by the specification in the absence of reference to a subset of amino acid sequences comprising the domains to which the functional properties of the peptides have been ascribed. While the specification discloses that a preferred peptide 3 is a compound of formula I (see page 3, second paragraph), it provides no guidance as to which amino acids might comprise the minimum residues which retains any enabled functional property peculiar to the instant polypeptides. One would not have a reasonable expectation of successfully making a representative number of amino acid substitutions in peptide 3 such that the resulting peptide would have the desired biological activity consistent with the scope of the claims. Additionally, one would reasonably expect that making variants of the instant peptide would abolish activity because activity is determined not only by primary sequence, but also by three-dimensional structure, as, for example, is the case for the ligand binding site of a receptor or for a catalytic site of an enzyme. Any arbitrary variant of the amino acid sequence of SEQ ID NO:1, 7-14 would not be expected to confer the desirable inhibition of chemokine-induced cell migration activity. Therefore, in the absence of delimiting amino acid

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sequences that make up the functional domains of the instant peptides, a person of ordinary skill in the art would be unable to make variants and derivatives of the amino acid sequences embraced by the claims without undue experimentation to determine which amino acids retain the desirable biological activity.

Furthermore, Applicant is encouraged to review the discussion of 35 U.S.C. § 112, first paragraph, in a recent CAFC decision, Genentech, Inc. v. Novo. Nordisk, 42 USPQ2d, 100 (CAFC 1997), in which the decisions in In re Fisher, Amgen Inc. V. Chugai Pharmaceuticals Co. Ltd., and In re Wands were considered as the controlling precedents in determining enablement issues where protein and recombinant DNA issues are concerned. These decisions have been relied upon in the instant rejection and by the Court because they show that the judicial interpretation of the first paragraph of 35 U.S.C. § 112 requires that the breadth of claims must be based upon the predictability of the claimed subject matter and not on some standard of trial and error. Unless one has a reasonable expectation that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the instant specification provides sufficient guidance to permit one to identify those embodiments which are more likely to work than not, without actually making and testing them, then the instant application does not support the breadth of the claims. The instant specification does not provide the guidance needed to predictably alter the amino acids of "chemokine peptide 3", with any reasonable expectation that the resulting peptide will have the desirable peptide activity. To illustrate this issue, the Examiner has cited Cunningham et al. who teaches that in a strategy called alanine-scanning mutagenesis, replacement of a cluster of amino

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acids with alanine in human growth hormone (hGH), resulted in more than four times lower binding affinity to the hGH receptor (see page 1081, abstract, lines 1-8). Alanine was chosen as the replacement residue because alanine eliminates the side chain beyond the β carbon, yet does not alter the main-chain conformation (as can glycine or proline) nor does it impose extreme electrostatic or steric effects (page 1081, column 1, lines 18-23), and in general, alanine is the most abundant amino acid frequently found in both buried and exposed positions in proteins (page 1081, column 1, lines 24-27). However, as disclosed by Cunningham, single substitutions by alanine in 42 out of the 65 hGH mutants resulted in tertiary structure changes reflected by changes in binding affinity of the mutants to the receptor, because side chains of amino acids are important for modulating binding of ligands to receptors (page 1081, column 1, lines 14-17; page 1081, Figure 1 and page 1082, Table 1). The instant specification does not outline residues which are considered conservative. This is not adequate guidance as to the nature of the derivatives or variants of the peptide molecules that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Furthermore, the claims do not indicate the number of conservative substitutions i.e. there is no upper limit to the amount of substitutions. To further illustrate this point, the Examiner has cited George et al. (1988) which discloses that "sequence-comparison methods will not be able to assess biological relatedness until the structure/function problem is more clearly understood" (see page 145, last 4 lines of column 2) and that "statistical measures of similarity do not necessarily reflect biological significance" (see page 146, column 1, lines 11-13). Therefore Applicants have not presented enablement commensurate in scope with the claims.

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9. Claims 1, 3-12 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "chemokine peptide 3", which is vague and indefinite in the absence of a specific definition for such in the instant specification. There are only preferred embodiments for chemokine peptide 3 recited in the specification (see page 3, second paragraph), which are exemplary, and therefore the metes and bounds of the claims are unclear.

Claims 3-12 are rejected as vague and indefinite insofar as they depend on claim 1 for this limitation.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10a. Claims 1, 3-4, 6-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Rollins et al. (U.S. Patent No. 5,459,128) .

Rollins et al. teach human MCP-1 derivatives in which the wild-type MCP-1 is modified in one or more of the following: (a) the 28-tyrosine is substituted by aspartate, (b) the 24-arginine is substituted by phenylalanine, (c) the 3-aspartate is substituted by alanine, and/or (d) the 2-8 amino acid sequence is deleted (see abstract; column 2, lines 15-26; column 4, lines 18-67; column 5, lines 1-67). Therefore, the MCP-1 derivative of Rollins et al. meets the limitations of claims 1, 3-4, 6-7,

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of a of a chemokine peptide 3 variant of MCP-1, which is a CC chemokine, because if one assumes the term chemokine peptide 3 means a preferred peptide 3 of the formula set forth on page 3, second paragraph, of the instant specification, the claims are anticipated by Rollins et al. This 35 U.S.C. 102(b) rejection is based on the premise that there is nothing in the instant specification, that discloses what elements from the instant prior art protein are absent, such that the prior art protein is excluded and not anticipated by the instant claims. In the absence of clarity in the specification, regarding the definition of chemokine peptide 3, the prior art MCP-1 derivative anticipates claims 1, 3-4, and 6-7.

10b. Claims 1 and 8-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Clark-Lewis et al. (1993) .

Clark-Lewis et al. teach human PF4 derivatives in which the wild-type PF4 is modified by introduction of the ELR sequence at the N-terminus and found that the modified protein was a potent neutrophil activator and attractant (see abstract; page 3575, column 2, first paragraph and Figure 2; page 3576, column 1, paragraph 1-2 and Figure 3). Therefore, the PF4 derivative of Clark-Lewis et al. meets the limitations of claims 1, 8-10, of a of a chemokine peptide 3 variant of PF4, which is a CXC chemokine, because if one assumes the term chemokine peptide 3 means a preferred peptide 3 of the formula set forth on page 3, second paragraph, of the instant specification, the claims are anticipated by Clark-Lewis et al. This 35 U.S.C. 102(b) rejection is based on the premise that there is nothing in the instant specification, that discloses what elements from the prior art protein are absent, such that the instant prior art protein is excluded and not anticipated by the instant claims. In

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the absence of clarity in the specification, regarding the definition of chemokine peptide 3, the prior art PF4 derivative anticipates claims 1, 8-10.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (703) 308-4229. The examiner can normally be reached on Monday-Friday from 8:00AM to 4:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Prema Mertz
Prema Mertz Ph.D.
Primary Examiner
Art Unit 1646
March 26, 1999